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14. ABSTRACT
This report represents the sixth in a multi-year effort to improve outcomes in patients with traumatic brain injury (TBI) utilizing human and animal models. The first two years focused on infrastructure development, development of a basic science protocol, development and institution of two human use protocols, staff acquisition, equipment purchase and development of a Brain Resuscitation Registry (BRR) to provide structure and linkage capabilities for data collection and outcome reporting. Year 3 accomplishments included the ongoing enrollment of human use protocol subjects focusing on the inflammatory process following TBI and vital sign response to trauma, development and implementation of 2 retrospective human use protocols, processing of specimens, further development of the BRR and initiation of the basic science model including both small and large animal models of polytrauma. During Year 4 the existing human use protocols concluded data collection and neared finalization of data analysis, and a new protocol was proposed. Progress continued in BRR development and reporting, and the animal sub-project neared completion. Year 5 saw completion of data analysis for the Cytokines and Animal sub-projects, ongoing analysis of the Vital Signs sub-project, and continued development of the final human use sub-project. Year 6 focused on implementation and data collection for the final human use protocol, and finalization of data analysis for the Vital signs sub-project.

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Traumatic Brain Injury (TBI); vital signs; cytokines; pre-hospital care; polytrauma

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INTRODUCTION

Traumatic Brain Injury (TBI) is the primary cause of trauma mortality in both civilian and military populations, a major source of long-term disability world-wide and a substantial independent cause of death in the U.S. The dominance of TBI in trauma epidemiology is due to our inability to treat primary central nervous system injury and the realization that the phenomenon of secondary brain injury (pathology at the metabolic, cellular, vascular and tissue levels) begins within seconds after the primary trauma and plays a profound role in the subsequent evolution of TBI. This multi-year effort to improve outcomes in TBI patients focused creation of an infrastructure necessary to associate elements of care for the TBI patient with specific and relevant outcomes, including establishment of a centralized Brain Resuscitation Registry (BRR) for data capture, deployment of equipment to capture continuous pre-hospital and in-hospital vital signs, and development of human use and basic science models.

Targeted efforts over the life of the project have included: a human use protocol to examine the contribution of inflammatory cytokines after TBI, retrospective protocols to examine the contribution of oxygen delivery and surgical timeframes to outcome from TBI, and both small and large animal sub-projects of controlled cortical impact. During the fourth year of the project, the existing human use protocols completed data collection and focused on analysis, and an additional human use protocol was identified and submitted for approvals. The animal models neared completion of development and the BRR continued development with a focus on reporting structure. A no-cost extension for the 5th year of the project allowed for finalization of data analysis for sub-projects initiated in years 1 through 4 and further development and IRB approval of a final human use sub-project. A 20 month no-cost extension was approved in September of 2012, to allow for completion of the final human use protocol. The sixth year of the project has focused on implementation of the final human use sub-project. Primary data collection is now nearing a close for this sub-project with subject follow-up data collection projected thru early 2014.

BODY

This is the annual report for Year 6 of a multi-year project. Table 1 below reflects the adjusted Project Milestones Timeline based on the actual funding award date of September 17, 2007. Start and finish date columns reflect target timelines while subsequent columns reflect actual task completion dates. Research progress is further summarized by the itemized sub-projects following the table.

Table 1: Timeline

Activity Name	Target Completion	Actual Completion
Vital Signs Sub-project		
**Complete matching of 2009 cases	16-Oct-2010	1-Oct-2010
**Development of real-time ICU Team View	16-Oct-2010	1-Oct-2010
**Development of TBI prediction methods and algorithms	16-Oct-2010	On-going
**Complete matching of 2010 cases	31-Mar-2011	01-Apr-2011
***Initial IRB approvals*	31-Jan-2008	02-Apr-2008
Cytokines Sub-project		
**Purchase of final assay kits	15-Apr-2011	01-Dec-2010
**Completion of assay processing	15-Apr-2011	04-Jan-2011
**Completion of data analysis	15-Feb-2012	15-Mar-2012
***Initial IRB approvals*	31-Jan-2008	29-Jul-2008
Brain Resuscitation Registry		
**Implementation of reporting process	15-Jan-2011	12-Jan-2011
**On-going refinement of reporting process	15-Oct-2011	01-Jul-2012
Retrospective Subprojects: **TBI and Fracture Fixation** *and* **TBI, Oxygenation and Outcomes**		
**Submission of abstracts	15-Jan-2011	04-Jan-2011
**Manuscript submission	1-Nov-2011	01-Apr-2012
***Initial IRB approvals*	15-Jan-2010	29-Mar-2010
Animal Subprojects		
**Continue development of rat polytrauma model	16-Oct-2010	01-May-2011
**Initiate rat protocol	15-Apr-2011	01-May-2011
**Completion of data collection	15-Sept-2011	01-Feb-2012
**Initiate pig protocol	15-Jan-2011	01-April-2011
**Completion of data collection	15-Sept-2011	01-Oct-2011
**Obtain CCI device		10-Jan-2011
***IRB approvals*	01-Oct-2007	26-Feb-2008
TCD and BAM sub-project		
**Submission of protocol to IRB	16-Oct-2010	21-Feb-2011
**Submission of protocol to USAMRMC	30-Nov-2011	05-April-2011
**Initiate protocol	24-Sep-2012	18-Oct-2012
**Complete Subject Enrollment	24-Sept-2013	
**Complete Follow-up Interviews	24-Mar-2014	
**complete Analysis and final reporting	24-May-2014	
***UMB IRB approval*		25-Mar-2011
***USAMRMC HRPO approval*		19-Dec-2011

All human sub-projects have received IRB approval from the University of Maryland (UMB), IRB and the USAMRMC ORP, HRPO prior to implementation.

Sub-project 1: Vital Signs Data in Trauma Patients

This project was initially approved by UMB, IRB and USAMRMC ORP, HRPO upon continuing review on 2/21/08. This study was then re-assigned to the current project "Early Support of Intracranial Perfusion," on 2/26/08.

During Year 1 several amendments were made to the project including a waiver of informed consent. An amendment was also approved in October 2010 to increase subject enrollment to a total of 14,000 subjects. The most recent approved annual renewal for this protocol was approved for continuation on 10/24/12 by UMB IRB and acceptance memorandum received from USAMRMC ORP, HRPO on 12/06/12 on 12/07/12.
The continuing renewal for the upcoming year was submitted to UMB IRB on 10/5/13 and we are awaiting approval.

Data collection and analysis for this sub-project are now complete. Final abstracts and manuscripts are in process. We anticipate closing the IRB protocol for this project by the end of the year.

The Vital Signs Data sub-project served as the foundation for three separate projects currently funded by USAF: "Continuous non-invasive monitoring and the development of predictive triage indices for outcomes following trauma" (FA 8650-11-2-6D01)PI: Colin Mackenzie, "Predicting blood product needs using pre-hospital vital signs" (FA 8650-11-2-6142)PI: Colin Mackenzie, and "Comparison of Automated and Manual Recording of Brief Episodes of Intracranial Hypertension and Cerebral Hypoperfusion and their Association with Outcome after Severe Traumatic Brain Injury (TBI)(FA8650-13-2-6D15). PI: Peter Hu, PhD, Deborah Stein MD and USAF PI: Col. Raymond Fang, MD

<u>Pre-hospital Vital Signs Data Collection (VSDC) system</u>

During Year 1 emphasis was placed on the development of equipment and working with pre-hospital providers to expand capabilities to obtain pre-hospital vital signs (VS) data.

Year 2 focused on further development of pre-hospital VS analysis to allow auto cleaning of VS artifacts. Critical episodes of hypoxia (SpO2 <95%, <90% <75%, hypotension (SBP<90; <100 mmHg) and tachycardia (HR>120, >110,>100 bpm) were identified. Available pre-hospital cases were linked with trauma registry data for identification of outcomes such as mortality, hospital /ICU length of stay, admit and discharge Glasgow Coma Scale (GCS) score, brain injury status (AIS-head), and ISS. In addition, review of medical records was completed to identify pre-hospital LSI (life saving interventions) and in-hospital emergency LSI during the first 4 hours.

During Year 3 a new LifePack system was introduced, and efforts focused on continued retrieval of these data and matching to potential subjects. Analysis was initiated based on vital sign waveform data collected in the pre-hospital management and in the first 60 minutes after admission to identify trends and prediction value of waveforms as compared to need for LSIs and outcomes.

During Year 4, approximately 250 pre-hospital VS case data were collected and matched with in-hospital Shock Trauma Center (STC) patient records. One hundred ninety –nine records were matched to STC patients and we were able to match 175 (88%) of these cases with in-patient and trauma registry outcomes data. The charts are currently being searched to obtain the pre-hospital run sheets and the timing and occurrence of LSIs. Once the data set has been validated then our existing outcome prediction software will be used to determine specificity and sensitivity (area

under Receiver Operator Characteristic curve) of LSIs and outcome measurements.

Also during Year 4 a new proposal based on this work, *Continuous Non-Invasive Monitoring and the Development of Predictive Triage Indices for Outcome following Trauma* (U of MD PI Colin F Mackenzie) was funded by USAF (FA 8650-11-2-6D01).

During Year 5, previously collected TBI patient VS data sets were utilized to develop machine learning models for prediction of morbidity at 3 months (GOSE) and mortality. The results of this analysis were presented at the International Machine Learning Conference in Berlin Germany on July 15/16, 2012 and submitted for publication. Efforts have also focused on the development of imputation methods for estimating missing ICP values in VS data sets, providing a potentially a critical stream of measurements for guiding clinical interventions and monitoring traumatic brain injuries.

<u>In-hospital Vital Signs Data Collection (VSDC) system and Shock Trauma Physiological (STP) Registry</u>

A limited system for VS data collection was in existence prior to the reassignment of this sub-project to the larger study. Therefore, emphasis in Year 1 was on system upgrades and expansion of VSDC capabilities. Expansion of the VSDC system from initial location in the Trauma Resuscitation Unit (12 admission bays and 6 operating bays) to a total of 54 critical care bays/beds also occurred during Year 1. Data mining was then initiated and preliminary algorithms were developed.

During Year 2 the VSDC system was further developed. Due to the low return on consent forms from prospective subjects, an amendment for a waiver of consent was submitted and approved by both UMB and USAMRMC.

In Year 3, based on the gap analysis, our research findings demonstrated the following:

1) The dose of patient VS above or below a critical limit (SBP<90, ICP>30, CPP<50 etc.) was determined to be a better predictor than the signal value alarm for patient outcomes (mortality, length of stay and 3, 6, 12 month GOSE).
2) It is difficult to quickly identify the patterns of multi-VS critical episodes at a glance for the duration of 12/24 hours.
3) For real-time ICU management it is important to show a quick overview of the patient in the unit. To address the above challenges we developed a real-time ICU Team View (ICUTV) which provides at-a-glance views of the 12 bed ICU VS trends and critical episodes. The ICUTV was deployed at the STC Neuro Trauma ICU with secured access made available to the remote physician office.

During Year 3, development of computer assisted auto patient physiological (VS) data identification software was also completed and introduced. This software facilitated the matching of 99.2% of the trauma admissions and the ultimate enrollment of 4,995 study subjects meeting study criteria. With improvements in the ability to accurately identify study subjects, a protocol modification is planned for the first quarter of Year 4 to increase the number of data sets available for analysis

By the end of Year 4, pre-hospital and admission VS data for more than 13,000 trauma patients admitted to the Shock Trauma Center (STC) in 2009 and 2010 were obtained from the trauma registry and analyzed using Receiver Operator Characteristic curves to predict the need for the LSI of a blood transfusion. Blood bank records identified those patients in this cohort who

were alive on arrival, acutely hemorrhaging, and received blood and blood products within the first 24 hours. Findings indicated that pre-hospital and STC admission Shock Index (SI = heart rate/systolic blood pressure) had an 86% sensitivity and 81% specificity to predict blood and blood product use within 24 hours of STC admission (area under the Receiver Operator Characteristic curves of 0.72 and 0.78 respectively)**.** The importance of this finding is that a 20-30 minute 'heads up' in advance of casualty arrival, obtained by automated SI decision- assist communicated from the field to the blood bank, would allow for a full range of blood products to be thawed or otherwise processed to supply coagulation factors such as plasma and platelets in near equivalence with red cells.

During Year 5, on-going analysis continued utilizing this data set in the development of prediction models as described. During Year 6, final manuscript preparation was initiated. The protocol for this sub-project will be closed in the next 6 months as all analysis will be complete.

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

The protocol was initially submitted to UMB IRB on 3/20/08 and after requested revisions the final protocol was approved by UMB, IRB on 7/28/08 and USAMRMC ORP, HRPO on 7/29/08. The most recent annual renewal for this protocol was submitted to UMB IRB on 01/17/12 and approved for continuation on 01/19/12. The continuing review report was submitted to USAMRMC ORP, HRPO on 03/07/12 and the acceptance memorandum received on 06/04/12. In December 2012 a closure report was submitted to UMB IRB and the protocol has now been closed.

This sub-project is now complete.

Year 1 focused on the standardization of policies and procedures for recruitment, specimen and data collection. The sub-project coordinator was assigned and identified research staff trained on recruitment and specimen/data collection procedures. Standardization of procedures for handling of collected specimens and specimen storage was completed during the fourth quarter of Year 1. Screening for this sub-project was opened on 8/20/08.

At the close of Year 2, 42 subjects had been enrolled in the study, with one screen-fail and one subject withdrawn. Eight of the 42 subjects expired due to their injuries. Preliminary analysis has focused on the first 30 cytokines subjects to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and outcome (Mortality, hospital length of stay, surgical management, 3 Month and 6 Month GOSE). At the close of Year 2 sufficient assay materials required for processing the first 30 study subjects were ordered.

Enrollment of the 50 subject target was completed in January 2010 and follow-up thru 1 year post injury was completed on all available subjects in Year 4 (January 2011). At the conclusion of the follow-up period, 10 (20%) of the 50 subjects had expired due to their injuries. Of those remaining, 38 subjects completed their 3 month follow-up, 36 completed their 6 month follow-up and 31 completed a 12 month follow-up interview. One subject declined further follow-up upon contact at 6 months, and two subjects were unable to be reached after multiple attempts.

During Year 3, remaining assay materials were acquired, analysis of serum samples for the first half of the study cohort was completed and initial processing of all CSF samples

completed. At the close of Year 4, assays for all serum and CSF samples had been processed and analysis on the complete grouping was near completion. Detailed analysis on all data components and their relationship to specific outcome measurements had been initiated.

Analysis of the data set reached completion during Year 5, and all manuscripts related to this sub-project have been published in peer-reviewed journals.

Complete the Brain Resuscitation Registry network architecture

During Year 1, secure web-based trauma registry containing clinical patient information for trauma patients was established. Year 2 focused on the continuing development of the network architecture. Links were established to automate the extraction of patient data needed to profile, enroll, manage and analyze current study populations. Study protocols were centralized and automated allowing for the establishment of communication between studies. Screens were added to the registry for current trauma patients to accommodate selection and clinical data management. The Cytokines sub-project served as the test study for these processes and for the training of research staff.

Year 3 progress included the installation of a dedicated server which, along with the purchase of dedicated screening tablets, allowed the implementation of a fully active automated screening process. Screening of all TRU Patients is now tracked through the system. Addition of a minimum required data feature ensures that key trauma data points are captured before the system will permit a patient to be closed out even if he/she is not suited for any study. Adjustments to the rules module (and its interface) were finalized so that it may accurately filter the required include/exclude criteria for the studies currently in the system.
The system restricts users on a study-by-study basis and can permit view only roles or other access restrictions based on the user's job responsibilities and study privileges. Reporting has continued to be developed. There are now real time screening statistics on each study that provide information on how many relevant patients were screened and the breakdown of why candidates were ineligible for a particular study.

Enhancements during Year 4 included security and workflow processes enhanced to allow a secondary screening phase if a study requires it. This permits study coordinators to distribute more intensive data collection responsibilities to specific users without holding up the patient in studies for which they have already been excluded. A dedicated interface is being installed between the main clinical information and the BRR. This will allow more autonomy and stability as it will not be dependent on ancillary systems for ADT data.

The outcomes survey process is now fully up and running allowing bi-weekly imports of completed outcome surveys. These surveys are administered on ScanTron forms that are then imported into the BRR and linked to the patients' initial screening and treatment data. The process has been enhanced to merge with the scheduling system so that the survey forms are pre-printed with the patient information prefilled out, thus making the visit matching process much more accurate and allowing for better auditing of staff compliance. Additionally, instant evaluation of the outcomes forms and coordination between the Shock Trauma clinic and rehab clinics is helping to aid in providing patients with immediate referrals for follow-up services.

A reporting database module is being developed that joins the three systems of the trauma registry, the Brain Resuscitation Server and the outcomes data. This will allow adhoc querying

and data mining of anonymous case histories by researchers. It will also allow access of qualified users to full queries within the scope of their study protocols and regulations. An intranet Wiki server has been set up allowing documentation of the Brain Resuscitation System for both technical and user personnel which permits easy online access to all help manuals.

During Year 5, the expansion of the registry to support a consistent and standardized approach to research efforts at the conclusion of this funding was continued. A reporting "Data Warehouse" that will receive admission and screening data and ultimately link to treatment information and follow-up data continues to evolve. Efforts were also initiated to develop a returning patient notification module to monitor readmissions for previous study subjects.

In Year 6 the research registry continues to be used for data collection on all patients arriving in the trauma receiving unit and facilitates information exchange between work shifts. Development continues on the reporting "Data Warehouse" that will receive admission and screening data from the research registry and link them to the treatment information and follow up outcomes data, providing an "Incident to Recovery" range of data.

The registry will continue to be used for new research projects in the future as the method for standardizing and evaluating the data collected for the screening process, encompassing virtually all research efforts and not just those under this project.

Retrospective Sub-projects

Two new retrospective sub-projects were initiated in Year 3, in preparation for prospective studies. Both were approved by UMB IRB as exempt protocols on 02/24/10 and approved as exempt by USAMRMC on 03/29/10

Traumatic Brain Injury and Fracture Fixation

Traumatic Brain Injury, Oxygenation and Outcomes

Traumatic Brain Injury and Fracture Fixation

The records for 167 consecutive TBI subjects with femoral shaft fractures between 06/2002 and 06/2009 were reviewed and analysis was completed. All patients with a head AIS > 2 who survived at least 12 hours beyond admission were included in the study.

One abstract based on these analyses has been presented and a manuscript was submitted.

Traumatic Brain Injury, Oxygenation and Outcomes

Data for 1660 consecutive TBI subjects admitted between 06/2002 and 06/2009 were reviewed to identify predictors of outcome based on FiO2 delivery and analysis was completed.

Two abstracts have been presented based on this work and a manuscript was published

Sub-project 3: Animal Model of Brain Injury

The animal use protocol described in the initial statement of work was approved by the UMB IACUC on 9/21/07. It was subsequently submitted to the USAMRMC Animal Care and Use Review Office (ACURO) on 11/27/07. In response to the review by the USAMRMC ACURO, a revised protocol was submitted on 2/25/08 and approved by USAMRMC ACURO on 2/26/08.

During the course of Year 2, the model was changed to a large and small animal polytrauma model of contusional brain injury (controlled cortical impact) plus hemorrhagic shock. This change was necessary due to challenges in finding a vendor for the device necessary for conducting the penetrating brain injury paradigm with large animals, and feedback from the review of the last annual report that a large animal model of polytrauma caused by TBI plus hemorrhagic shock would be more clinically translational than that of a rodent model. A revised SOW was developed using a combination of both controlled cortical impact plus hemorrhagic shock with adult male Sprague Dawley rats and with adult male Hanford miniature swine (Sinclair Bio-resources).

In Year 3, the pig CCI model was finalized and approvals received by both UMSOM and ACURO. Development, equipment procurement and initiation of the two planned small and large animal model protocols proved more challenging than originally identified. Over Year 3 the original goal of developing a rat polytrauma model consisting of controlled cortical impact (CCI)-induced contusional brain injury plus hemorrhagic shock was reached. As expected the combination of hemorrhagic shock plus CCI results in death to cells in the cerebral cortex (cortical lesion volume) that is significantly greater than that obtained with CCI alone. One consequence of hemorrhagic shock is a systemic inflammatory reaction that can result in multiple organ failure. While the degree of hypotension induced in our model is not sufficient to produce multiple organ failure, it is sufficient to induce systemic inflammation. We hypothesized that this reaction is responsible for the greater cortical lesion volume observed with the polytrauma model compared to that with CCI alone. At the end of Year 3 the CCI device for use in both the large and small animal models was purchased.

Mini-pig model

Year 4 efforts tested the above hypothesis through a series of directed experiments. During this period, we sought to establish a dose-response relationship between CCI impact depth and cortical lesion volume, using a large animal model consisting of mini-pigs. Progress on this aim was delayed by the difficulty in finding a company that would supply an appropriate CCI device and stereotaxic head-holder for pigs. The device was ordered late in Year 3 and was received during Year 4.

By the close of Year 4, the research team had successfully altered the degree of injury delivered with the new cortical impact device. While initial impact parameters were based on previously published data, experiments performed in our laboratory demonstrated that a cortical impact of 11 mm depth delivered at 5.0 m/s by our newly constructed CCI device results in a ruptured dura with herniated brain matter. In addition to widely evident subdural hemorrhaging, a depth of 11 mm results in widespread subarachnoid hemorrhaging on both the injured as well as the uninjured cerebral hemispheres (frontal, parietal, temporal and occipital) and cerebellum. An impact depth of 7 mm delivered at 5.0 m/s resulted in a moderate injury where the dura was left intact with no herniation of brain matter. Although there was subdural hemorrhaging localized to the impact site on the ipsilateral hemisphere, there was no evidence of subdural

hemorrhaging on the contralateral hemisphere and minimal bilateral subarachnoid hemorrhaging was contained to the cortical temporal and occipital lobes.

Activation of inflammatory processes and neuronal degeneration as evidenced by FJB positive cells, condensed chromatin, loss of NeuN immunoreactivity and axonal beading occurred within 4 hours following 7mm controlled cortical impact in the cavity penumbra as well as in the ipsilateral hippocampus.

Rat model

During late Year 4 and into Year 5, over 60 rat experiments with the device were completed. After many months of testing different variables, we have finalized the model to include a 1.25 mm depth of cortical impact followed by 30 min of hemorrhagic shock (mean arterial blood pressure (MABP) between 35 and 40 mm Hg. As a simulation of war fighter polytrauma in the field, rats are then provided pre-hospital resuscitation using HEXTEND injections to achieve MABP of 55-65 mm Hg over one hour. Animals then receive their shed blood at the beginning of their hospital-phase resuscitation and are slowly taken off isoflurane anesthesia one hour later.

The fixed brains were then stained with Fluoro Jade B (FJB) for determination of total cortical infarct volume, using stereologic analysis of 1 out of 24, or 6 sections per brain. The mean percentage of the total infarct plus cortical penumbra containing degenerating neurons is 22 ± 3 % (n = 6) for both hemispheres. Clearly, this polytrauma model produces severe TBI, but without significant mortality under these conditions. Based on the relatively consistent results obtained with these pilot experiments we then completed randomized, blinded tests to determine if administration of sulforaphane, a drug found to be neuroprotective after CCI alone, is also neuroprotective for CCI plus hemorrhagic shock. Analysis of the results was completed during Year 5 and an abstract presented as well as a manuscript published based on the findings.

All work on this sub-project was completed by the end of Year 5.

New sub-project: Transcranial Doppler and Brain Acoustic Monitoring

At the end of Year 3, a protocol was developed to evaluate two non-invasive tools for assessment of cerebral perfusion and vasospasm in patients with severe TBI. This protocol will use both Transcranial Doppler (TCD) screening and the Brain Acoustic Monitor (BAM) to study the incidence of vasospasm in patients with severe TBI. Using well-established criteria for vasospasm detected with TCD, the BAM device data will be analyzed to determine the ability to apply this non-invasive bedside tool to improve diagnostic capabilities in patients with severe TBI. Forty patients with severe TBI will be enrolled in this pilot study. Daily TCDs and BAMs will be obtained for 7 days following injury. Dr Kevin Sheth will be joining the research team as a co-investigator for this study. The protocol was initially approved by UMB IRB in March 2011, and requested USAMRMC HRPO modifications approved by UMB IRB in June 2011. USAMRMC requested UMB IRB determination for non-significant risk device, which was received on 12/05/11. And USAMRMC HRPO issued the approval memorandum on 12/19/11. At the time of continuing review with UMB IRB, modifications were required to bring the consent form in line with a new UMB template. These modifications were completed and approved on 03/12/12, and the continuing review was approved by UMB IRB on 03/14/12. The annual continuing renewal for this protocol

was submitted UMB IRB in February 2013 and received approval on 02/11/13. The continuing review report was submitted to USAMRMC ORP, HRPO on 03/29/13 and the acceptance memorandum was received on 04/04/13.

Recruitment for this sub-project began on 10/18/12. To date 20 have been enrolled; 17 subjects completed at least 5 days of TCD and BAM follow-ups. Two subjects ultimately expired due to their injuries. Long-term follow-up data collection was initiated in February 2013. Thirteen subjects have become eligible for 3 month follow-up and data has been successfully obtained on 10 subjects. Nine subjects have become eligible for 6 month follow-up and data has been successfully obtained on six subjects. Primary data collection is targeted to end in late 2013, to allow for collection of follow-up outcome data and completion of data analysis by the end of the current no-cost extension.

KEY RESEARCH ACCOMPLISHMENTS

Sub-project 1: Vital Signs Data in Trauma Patients

At the close of Year 1

- Enhanced the pre-flight patient Vital Signs data collection network
- Developed and expanded the in-trauma center VS data collection network to cover all critical care bays (TRU, OR, ICU)
- Developed and deployed a total pre and in-hospital VS data collection network
- Developed a basic VS data mining system to collect, process, and predict patient outcomes
- Established a road map for innovative prediction algorithm development

At the close of Year 2

- Completed the hospital/center based real-time patient physiological data collection network (covers all 90 trauma center beds)
- Developed a basic real time Shock Trauma Physiological (STP) Registry.

Key research findings include:

  - Continuous pre-hospital VS reviewed by 3 Subject Matter Experts (SME) identified more critical episodes (up to 300%) than Trauma Registry (TR).N=177
  - SME identified critical episodes (HR>120 bpm, SpO2<90, SBP<90mmHg) predicted outcome (mortality, length of stay, discharge GCS) better than TR. N=177.
  - Continuous pre-hospital VS better predicted emergency LSIs than TR (N=177)
  - EMS pre-hospital protocols may be monitored remotely in pre hospital care of TBI. (N=64)

At the close of Year 3

- Development of a computer assisted auto patient physiological (VS) data identification software, facilitating the successful matching of the 2008-2009 STC admission VS data for patients fitting enrollment criteria
- Continued development and refinement of continuous VS based prediction models
- Development of real-time ICU Team View (ICUTV), providing at-a-glance views of the 12 bed Neuro ICU VS trends

At the close of Year 3, a transition plan for the VS project was initiated. Information on the methods and strategies proposed to move the VS product to the next phase of development includes submission of a funding request to USAF to examine the Pulse Oximeter signal in more detail than is currently possible with infrastructure and equipment available under the current funding. In brief, the project seeks to identify, test and validate accuracy of algorithms, models and sensors to predict adverse events and the necessity for actionable therapeutic interventions including: hypoxemia, hemorrhagic shock, need for blood transfusion, chest tube insertion, airway management and other LSIs, and abdominal surgery to control hemorrhage.

At the close of Year 4

- Completion of case matching for 2010
- The project, titled “Continuous non-invasive monitoring and the development of predictive triage indices for outcome following trauma,” was funded by USAF (FA 8650-11-2-6D01); UM PI: Colin Mackenzie, USAF PI: Joseph J DuBose
- The project, titled “Traumatic Injury and Medical Evacuation – Patient Outcomes (TIME-PO), was funded by USAF ; USAF PI: David Power

At the conclusion of Year 5, the following fund was obtained or is anticipated as a result of preliminary work under this project

- For the project, titled "The Vitals Signs 'Genome Project'- Computational gene mapping to analyze continuous automated real-time vital signs monitoring data" was funded by USAF (MSA); UM PI: Deborah Stein
- The project, titled "Noninvasive intracranial pressure monitoring using advanced machine learning techniques" was funded by USAF; UM PI: Deborah Stein
- The project, titled "Fit to fly biomarkers after severe TBI" was funded by USAF (MSA); UM PI: Deborah Stein
- The project, titled "Predicting casualty blood product needs using pre-hospital vital signs" was submitted to USAFMSA and we are anticipating approval of funding in October 2012.

At the conclusion of Year 6, the following fund was obtained as a result of preliminary work under this project.

- "Comparison of Automated and Manual Recording of Brief Episodes of Intracranial Hypertension and Cerebral Hypoperfusion and their Association with Outcome after Severe Traumatic Brain Injury (TBI) (FA8650-13-2-6D15). UM PI/ Co-PI: Peter Hu, PhD, Deborah Stein MD

<u>Sub-project 2: Early Support of Intracranial Perfusion – Cytokines</u>

At the close of Year 2

- Recruitment of 42 study subjects

30 cytokines cases were used to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and TBI patient outcome (Mortality, hospital length of stay, time of craniotomy, 3 Month, 6 Month and 12 month GOSE). The findings are

- ICU ICP>20, 30 CPP<50 , 60 predict patient outcome better than patient charts VS.
- Combined ICP>20 and CPP<60 episodes predict outcome better than individual ICP and CPP.
- Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI.
- The "Brain Trauma Index": Dynamic 3-D scoring in the assessment of TBI
- Computerized patient vital signs charting method enhances real-time record keeping in ICU
- Heart rate variability is associated with intractable intracranial hypertension and cerebral hypoperfusion

At the close of Year 3

- Recruitment of targeted 50 subjects
- Preliminary processing of serum and CSF samples for all subjects
- Analysis of all samples and correlation to clinical markers of TBI severity
- Determination of serum and CSF biomarkers that predict worsening of cerebral hypoperfusion, intracranial hypertension, and cerebral hypoxia.

At the close of Year 4

- Data collection and longitudinal follow-up was completed
- Processing of serum and CSF samples was completed

At the close of Year 5

- Detailed analysis of all data points was complete, and as well as final manuscript preparation and submission

Between Sub-project 1 and 2 in the past 6 years, there have been15 peer reviewed journal manuscripts published, 42 abstracts and conference papers and 52 presentations at major trauma, anesthesiology, critical care, engineering and DOD conferences.

Sub-projects – Retrospective

TBI and Fracture Fixation

At the close of year 3, preliminary analysis completed, key findings include:

- Early femur fracture fixation in TBI subjects correlates with significantly reduced hospital and ICU length of stay
- Early definitive fracture stabilization has no detrimental effect on mortality and discharge GCS
- 1 abstract had been presented

At the close of Year 5

- 1 manuscript had been submitted for publication

TBI, Oxygenation and Outcomes

At the close of year 3, preliminary analysis nearing completion, early key findings include:

  - Hyperoxemia within the first 24 hours of hospitalization increases mortality and worsens short-term functional outcomes in TBI subjects.
  - Poor outcomes may be predicted by hypoxia within the first 24 hours of admission

At the close of Year 4,

- 1 abstract had been presented

At the close of Year 5,

- 1 additional abstract had been presented and 1 manuscript published

Sub-project 3: Animal Model of Brain Injury

At the close of Year 2

- A rat polytrauma model consisting of controlled cortical impact traumatic brain injury plus hemorrhagic shock had been successfully developed.
- Preliminary experiments performed with human cerebrospinal fluid samples indicate that they can be used in a new and novel assay that detects toxicity of these samples on culture cell lines, using cellular respiration and glycolysis as outcome measures

At the close of Year 3,

- Rat model for CCI plus hemorrhagic shock was finalized
- CCI device for both rat and mini-pig models was purchased

At the close of Year 4,

- Initiation of rat CCI model
- Initiation of mini-pig CCI model

At the close of Year 5,

- Rat and mini-pig CCI models had been completed including data analysis
- 1 abstract had been presented and 1 manuscript published based on the findings.

Sub-project: Transcranial Doppler and Brain Acoustic Monitoring

At the close of Year 6

- Recruitment of 20 subjects and outcome data collection completed on 6 subjects through 6 month follow-up.

REPORTABLE OUTCOMES

a) Presentations:

5th Annual Innovations in the Surgical Environment Conference, June, 2008

Lesson learned: developing in-fight patient vital-signs data collection network
Hu P, Handley C, Sen A, Seebode S, Conway A, Gens R, Kramer B, Jordan S, Webb R, Defouw G, Davies P, Ho D, Xiao Y, Mackenzie C, and Trauma Vital Signs Investigator and Associates (TVSI,TVSRA) Group

Can pre-hospital patient VS predict injury and intervention?
Hu P, Mackenzie C, Dutton R, Sen A, Floccare D, Bochicchio G, Xiao Y, Spearman J, Scalea T.

Challenges in developing real-time patient vital sign data collection network for trauma care. Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T.

American Telemedicine Association Annual meeting, April, 2008

Challenges in developing real-time in-flight patient vital-signs data collection system.
Hu P, Handley C, Seebode S, Conway A, Gens R, Mackenzie C, Ho D, Defouw G, Davies P, Floccare D.

Real-time Patient Vital Sign Data Collection Network for Trauma Care.
Hu P, Mackenzie C, Dutton R, Bochicchio G, Bochicchio K, Xiao Y, Spearman J, Scalea T.

American Society of Anesthesiologists Annual Conference, October, 2008

Continuous prehospital vital signs record identifies increased abnormalities/predicts interventions. Sen A, Hu P, Mackenzie C, Jordan S, Dutton R.

Correlation between ECG heart rate and pulse oximeter heart rate in prehospital aeromedical trauma transfer. Sen A, Hu P, Dutton RP, Mackenzie CF, Alexander M, Xiao Y.

American Medical Informatics Association Annual Symposium November, 2008

Automatic pre-Hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps. Mackenzie C, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T.

Statewide real-time in-flight trauma patient vital signs collection system. Hu P, Mackenzie C, Dutton R, Sen A, Xiao Y, Handley C, Ho D, Scalea T.

American Telemedicine Association Conference, April, 2009

Automated vital-sign recording identifies more critical episodes than chart abstraction. Hu P, Sen Y, Mackenzie C, Xiao Y, Jordan S, Dutton R, Scalea T, and Trauma Vital Signs Research Group (TVSG)

Can EMS protocols be monitored remotely in pre hospital care of traumatic brain injury (TBI)? Mackenzie C, Hu P, Sen A, Xiao Y, Jordan S, Dutton R, Scalea T.

16th World Congress of Disaster and Emergency Medicine, May, 2009

Continuous vital signs acquisition improves prehospital trauma triage. Sen A, Hu P, Mackenzie C, Jordan S, Xiao Y, Dutton R, Scalea T

In-flight vital signs blackbox for trauma care. Hu P, Mackenzie C, Dutton R, Sen Y, Xiao Y, Floccare D, Scalea T.

Video technologies in emergency health research in assessing quality of care: a study of trauma resuscitation milestones. Sen A, Hu P, Mackenzie C, Xiao Y, Dutton R.

American Association for the Surgery of Trauma AAST 2009 Annual Meeting, October, 2009

Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T.

American Society of Anesthesiologists ASA2009 Annual Meeting October, 2009

Real-time patient vital signs data registry for trauma patient care. Dutton R, Hu P, Xiao Y, Yeatts D, Mackenzie C.

High resolution ICP and CPP data better predict outcome of severe TBI. Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T.

American Medical Informatics Association AMIA 2009 Annual Meeting November, 2009

CPP/ICP dose index: Dynamic 3-D scoring in the assessment of TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Stein D, Scalea T.

Computerized patient vital signs charting method enhances real-time record keeping in ICU. Hu P, Akozer S, Lindell A, Liu K, Mitrou M, Gettings L, Stein D, Xiao Y.

Is there added value in continuous vital signs and video collection linked to trauma patient outcomes? Hu P, Mackenzie CF, Xiao Y, Seebode D, Wong M, Murdock K, Dutton R.

Society for Critical Care Medicine's 39th Critical Care Congress January, 2010

Heart rate variation is associated with intractable intracranial hypertension and cerebral hypoperfusion.
Kahraman S, Dutton R, Hu P, Stansbury L, Xiao Y, Stein D, Scalea T .

Critical care monitoring in the field: Pre-hospital continuous vital signs acquisition identifies best predictors of life-saving interventions in trauma patients. Sen A, Hu P, Mackenzie C, Dutton R, Jordan S, Xiao Y, Scalea T.

Cerebrospinal fluid levels of inflammatory mediators: association with outcome following severe traumatic brain injury. Stein DM, Murdock KR, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

Eastern Association for the Surgery of Trauma (EAST) 23rd Annual Scientific Assembly, January 2010

CSF levels of NSE and S100B in patients with severe TBI: correlation with clinical measures. Stein DM, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

6th Innovations in the Surgical Environment Conference March, 2010

Trauma center wide real-time patient vital signs data registry (VSDR) for improvement of patient safety. Hu P, Stein D, Xiao Y, Dutton R, Kahraman S, Yeatts D, Grissom T, Mackenzie C, Scalea T.

International Society for Magnetic Resonance in Medicine, May, 2010

Early diffusion changes following controlled cortical impact injury on a rat model. Zhuo J, Xu S, Racz J, Fiskum G, Gullapalli R.

Early metabolic changes following focal traumatic brain injury in rats measured using 1H MRS. Xu S, Roys S, Racz J, Shi D, Zhou J, Gullapalli R, Fiskum G.

2010 American Telemedicine Association Annual International Meeting May, 2010

High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes. Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T.

Association of University Anesthesiologists, Annual Meeting, May 2010

New uses of vital signs signals during resuscitation to triage, assess provider performance and predict outcomes.
Mackenzie CF, Hu PF, Ayan S, Woodford M, Floccare D, Scalea T.

NNS 2010: 28th Annual National Neurotrauma Symposium, June 2010

Early hypotension redefined in patients with severe TBI. Stein, DN, Brenner M, Sheth K, Hu P, Aarabi B, Scalea T.

Early fracture fixation improves select outcomes in TBI patients.
Brenner M, Stein DM, Hu P, Scalea T

8th Annual Neurocritical Care Society Meeting, September 2010

Association of CSF biomarkers and secondary insults following severe traumatic brain injury. Stein D, Kufera J, Lindell A, Murdock KR, Menaker J, Bochicchio GV, Aarabi B, Scalea TM.

Depth and duration of secondary insults predicts outcome in patients with severe traumatic brain injury. Stein D, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM

American Association for the Surgery of Trauma (AAST 2010) Annual Meeting, September 2010

Relationship of serum biomarkers to depth and duration of secondary insults following severe TBI.
Stein D, Lindell A, Murdock K, Menaker J, Keledjian K, Bochicchio G, Scalea T.

Dynamic three-dimensional scoring of cerebral perfusion pressure and intracranial pressure provides a Brain Trauma Index that predicts outcome in patients with severe TBI.
Kahraman S, Dutton R, Hu P, Stansbury L, Hess J, Xiao Y, Stein D, Scalea T.

American Society of Anesthesiologists Annual Scientific Meeting. October 2010

Continuously recorded SPO2 outperforms SPO2 from trauma registry in prediction of mortality. Woodford M, Mackenzie CF, Hu P, Dutton R, Scalea T.

Failure to achieve normothermia is not associated with worsened outcomes in brain injury patients. Grissom T, Hu P, Dubose J, Dutton R, Stein D.

American Medical Informatics Association Annual Symposium, November, 2010

Using vital signs network to improve patient safety: How many alarms are too many?
Hu P, Mackenzie C, Stein D, Chang W, Seebode S, Binder M, Kramer ME, Xiao Y.

Eastern Association for the Surgery of Trauma (EAST) 24th Annual Scientific Assembly, January, 2011

Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome following severe traumatic brain injury. Stein D, Hu PF, Brenner M, Sheth K, Aarabi B, Scalea TM.

Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

Traditional Systolic Blood Pressure Targets Underestimate Hypotension-induced Secondary Brain Injury. Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM

American Telemedicine Association Annual Meeting 2011

Pre-hospital hypoxemia and tachycardia trends better predict patient mortality than Trauma Registry values Hu P, Woodford M, Mackenzie CF, Dutton R, Seebode S, Liu K, Scalea T.

Brief Episodes of Abnormal Shock Index Predicts Mortality in Severe Traumatic Brain Injury. Hu P, Stein DM, Stansbury L, Brenner M, Kufera J, Xiong W, Jiao X, Scalea T.

Association of University Anesthesiologists Annual Meeting 2011

Real- time decision support during trauma patient resuscitation. Mackenzie CF, Hu PF, Stein D, DuBose J, Grissom T.

National Neurotrauma Society Symposium July 2011

Use of serum biomarkers to predict cerebral hypoperfusion following severe traumatic brain injury. Stein DM, Lindell A, Murdock K, Kufera J, Menaker J, Bochicchio G, Aarabi B, Scalea T.

Eastern Association for the Surgery of Trauma (EAST) Jan, 2012 conference

Computational Gene-Mapping to Analyze Continuous Automated Physiologic Monitoring data in Neuro-trauma Intensive Care. Stein D, Stansbury L, Hu P, Chang, Scalea T.

Pacific Coast Surgical Association, February 2012

Early hyperoxia worsens outcomes after traumatic brain injury (TBI). Brenner M, Stein D, Hu P, Kufera J, Woodford M, Scalea T.

National Capital Area TBI Symposium. Bethesda, May 2012

Hyperoxic versus normoxic resuscitation in a rat polytrauma model of TBI plus hemorrhage shock. Proctor, JL, Pan Y, Gupta E, Bordt E, Fiskum, G.

International Conference on Machine learning and Data Mining MLDM 2012, Berlin, July 2012

Outcome prediction for patients with severe traumatic brain injury using permutation entropy analysis of electronic vital signs data. Kalpakis K, Yang S, Hu P, Mackenzie C, Stansbury L, Stein D, Scalea T.

Neurotrauma 2012 Symposium, Phoenix, AZ, July 2012

Timing of Secondary Insults Following Severe Traumatic Brain Injury. Stein DM, Brenner M, Hu P, Zhu XS, Stansbury LG, Aarabi B, Scalea TM.

25th IPPR Conference on Computer Vision, Graphics and Image Processing, Taiwan, August 2012

Utility of 3-Dimensional ROC in using vital signs signal for blood transfusion. Chang CI, Hu P, Chen SY, Mackenzie C, Stansbury L, DuBose J, Scalea T

Military Health System Research Symposium (MHSRS) / ATACCC, Aug 2012

How Can We Reduce Transient Monitor Alarms in Trauma Resuscitation Units? Hu P, Chiu W, Mackenzie C, Miller C, Fang R, Xiong W, Hu E, Stein D, Scalea T.

American Association for the Surgery of Trauma (AAST) Annual Conference, September 2012

Timing of Intracranial Hypertension Following Severe Traumatic Brain Injury. Stein DM, Brenner M, Hu PF, Stansbury L, Aarabi B, Scalea T.

2012 IEEE Biomedical Circuits & Systems conference, Nov 28-30, Taiwan

Prediction of Mortality.
Slaughter G, Kurtz Z, desJardins M, Hu PF, Mackenzie C, Stansbury L, Stein DM.

ICMLA(International Conference on Machine Learning and Applications) 2012: Machine Learning Ensemble Methods and Applications track, December, Boca Raton, FL

Exploiting Representational Diversity for Time Series Classification
Oates T, Mackenzie CF, Stein DM, Stansbury LG, DuBose J, Aarabi B, Hu P.

Predicting Patient Outcomes from a Few Hours of High Resolution Vital Signs Data
Oates T, Mackenzie CF, Stansbury LG, Aarabi B, Stein DM, Hu P.

b) Publications (Journal or Proceedings):

Proceedings – abstracts and full length articles

Mackenzie CF, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T. **Automatic pre-hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps.** AMIA Annu Symp Proc. Nov 6:318-22, 2008

Hu PF, Handley C, Seebode S, Conway A, Gens Y, Mackenzie C, Ho D, Defouw G, Davies P, Floccare D. **Challenges in Developing Real-Time In-Flight Patient Vital-Signs Data Collection System**. Telemedicine and e-Health. 14(1)105, 2008

Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T. **Real-time Patient Vital Sign Data Collection Network for Trauma Care** . Telemedicine and e-Health. 14(1)62, 2008

Hu P, Handley C, Sen A, Seebode S, Conway A, Gens R, Kramer B, Jordan S, Webb R, Defouw G, Davies P, Ho D, Xiao Y, Mackenzie C **Lesson Learned: Developing In-Flight Patient Vital-Signs Data Collection Network** Proceedings of 5th Annual Innovations in the Surgical Environment Conference, 2008

Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T. **Challenges in developing real-time Patient Vital Sign Data Collection Network for Trauma Care** . Proceeding of 5th Annual Innovations in the Surgical Environment Conference. 2008

Sen A, Hu P, Dutton RP, Mackenzie CF, Alexander M, Xiao Y,. **Correlation between ECG Heart rate and Pulse Oximeter Heart rate in Prehospital aeromedical trauma transfer** Proceedings of the American Society of Anesthesiologists. 2008 .

Hu PF, Mackenzie C, Dutton RP, Sen A, Floccare D, Bochicchio G, Xiao Y, Spearman J, Scalea T. **Can Pre-Hospital Patient VS Predict Injury and Intervention?** Proceedings of 5th Annual Innovations in the Surgical Environment Conference, 2008

Sen A, Hu P, Mackenzie C, Jordan S, Dutton R. **Continuous Prehospital Vital Signs Record Identifies Increased Abnormalities/Predicts Interventions**. Proceedings of the American Anesthesiologists Annual Conference A1637. 2008

Sen A, Hu P, Mackenzie C, Jordan S, Xiao Y, Dutton R, Scalea T. **Continuous Vital Signs acquisition improves prehospital trauma triage.** Prehospital and Disaster Medicine 24(2):s139. 2009

Mackenzie C, Hu P, Sen A, Xiao Y, Jordan S, Dutton R, Scalea T,.**Can EMS Protocols be monitored remotely in pre hospital care of Traumatic Brain Injury (TBI)?** Telemedicine and e-Health, 15(1) S-72. 2009

Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T. **Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI** . Proceedings of American Association for the Surgery of Trauma (AAST) Annual Conference, 2009

Hu P, Sen A, Mackenzie C, Xiao Y, Jordan S, Dutton R, Scalea T, and Trauma Vital Signs Research Group (TVSG). **Automated vital-sign recording identifies more critical episodes than chart abstraction.** Telemedicine and e-Health, 15(1), S-73. 2009

Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T. **High resolution ICP and CPP data better predict outcome of severe TBI**. Proceedings of the American Society of Anesthesiologists Annual Conference A451154, 2009

Dutton R, Hu P, Xiao Y, Yeatts D, Mackenzie C. **Real-time patient Vital Signs Data Registry for Trauma Patient Care.** Proceedings of the American Society of Anesthesiologists Annual Conference A451833, 2009

Kahraman S, Hu P, Xiao Y, Dutton R, Stein D, Scalea T. **CPP/ICP Dose Index: Dynamic 3-D Scoring in the Assessment of TBI.** Proceedings of the American Medical Informatics Association AMIA-0061-A2009, 2009

Hu P, Akozer S, Lindell A, Liu K, Mitrou M, Gettings L, Stein D, Xiao Y. **Computerized patient vital signs charting method enhances real-time record keeping in ICU**. Proceedings of the American Medical Informatics Association - AMIA-0060-A2009, 2009

Hu P, Mackenzie C, Xiao Y, Seebode S, Wong M, Murdock K, Dutton R. **Is there Added Value in Continuous Vital Signs and Video Collection linked to Trauma Patient Outcomes?** Proceedings of the American Medical Informatics Association AMIA-0094-A2009, 2009

Hu P, Mackenzie C, Dutton R, Sen A, Xiao Y, Floccare D, Scalea T. **In-flight Vital Signs Blackbox for Trauma Care**. Prehospital and Disaster Medicine 24(2):s52-s53. 2009

Kahraman S, Dutton R, Hu P, Stansbury L, Xiao Y, Stein D, Scalea T. **Heart Rate Variability is Associated with Intractable Intracranial Hypertension and Cerebral Hypoperfusion.** Proceedings of The Society of Critical Care Medicine (SCCM) P.A160, 2010

Sen A, Hu P, Mackenzie C, Dutton R, Jordan S, Xiao Y, Scalea T. **Critical Care Monitoring in the Field: Pre-Hospital Continuous Vital Signs Acquisition Identifies Best Predictors of Life-Saving Interventions in Trauma Patients.** Proceedings of The Society of Critical Care Medicine (SCCM) p.A329, 2010

Hu P, Stein D, Xiao Y, Dutton R, Kahraman S, Yeatts D, Grissom T, Mackenzie C, Scalea T. **Trauma Center Wide Real-time Patient Vital Signs Data Registry (VSDR) for Improvement of Patient Safety** Proceedings of the 6th Innovations in the Surgical Environment Conference, 2010

Woodford M, Mackenzie CF, Hu P, Dutton R, Scalea T. **Continuously recorded SPO2 outperforms SPO2 from trauma registry in prediction of mortality.** Proceedings of American Society of Anesthesiologists Annual Scientific Meeting, 2010

Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T. **High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes** Proceedings of the American Telemedicine Association Annual Conference, May 2010

Stein DM, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM. **Depth and Duration of Secondary Insults Predicts Outcome in Patients with Severe Traumatic Brain Injury.** Proceedings of Neurocritical Care Society Meeting, September 2010

Stein DM, Brenner M, Sheth K, Hu PF, Aarabi B, Scalea TM. **Early hypotension redefined in the patients with severe traumatic brain injury.** Proceedings of 28th Annual National Neurotrauma Society Symposium June 14-17, 2010

Brenner M, Stein D, Hu P, Kufera J, Scalea T. **Early Fracture Fixation Improves Select Outcomes in Traumatic Brain Injury Patients** Proceedings of 28th Annual National Neurotrauma Society Symposium June 14-17, 2010

Grissom T, Hu P, Dubose J, Dutton R, Stein D**. Failure to achieve normothermia is not associated with worsened outcomes in brain injury patients.** Proceedings of American Society of Anesthesiologists Annual Scientific Meeting, 2010

Hu P, Mackenzie C, Stein D, Chang W, Seebode S, Binder M, Kramer ME, Xiao Y. **Using vital signs network to improve patient safety: How many alarms are too many?** Proceedings of American Medical Informatics Association Annual Symposium, 2010

Kahraman S, Dutton R, Hu P, Stansbury L, XiaoY, Stein D, Hess J, Scalea T. **Cerebral perfusion pressure/intracranial pressure dose index: Dynamic 3-D scoring in the assessment of Traumatic Brain Injury** Proceedings of American Association for the Surgery of Trauma (AAST) Annual Conference. September 2010

Stein D, Hu PF, Brenner M, Sheth K, Aarabi B, Scalea TM. **Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome following severe traumatic brain injury.** Proceedings of Eastern Association for the Surgery of Trauma (EAST) 24th Annual Scientific Assembly, 2011

Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM. **Traditional Systolic Blood Pressure Targets Underestimate Hypotension-induced Secondary Brain Injury**. *Proceedings of* Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly
M Brenner, D Stein, P Hu, J Kufera, M Wooford, T Scalea **Too much of a good thing? Early hyperoxemia worsens outcomes in TBI patients** Proceedings of Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

Hu P, Woodford M, Mackenzie C, Dutton R, Seebode S, Liu K, Scalea T. **Pre-hospital hypoxemia and tachycardia trends better predict patient mortality than Trauma Registry values** Proceedings of American Telemedicine Association Annual Meeting ATA 2011

Hu P, Stein D, Stansbury L, Brenner M, Kufera J, Xiong W, Jiao X, Scalea T. **Brief Episodes of Abnormal Shock Index Predicts Mortality in Severe Traumatic Brain Injury.** Proceedings of American Telemedicine Association Annual Meeting ATA 2011

Mackenzie C, Hu F, Stein D, DuBose J, Grissom T. **Real- time decision support during trauma patient resuscitation** Proceedings of a Association of University Anesthesiologists 2011

Stein D, Stansbury L, Hu P, Chang, Scalea T, **Computational Gene-Mapping to Analyze Continuous Automated Physiologic Monitoring data in Neuro-trauma Intensive Care** Proceedings of Eastern Association for the Surgery of Trauma (EAST)2011 .

Chang CI, Hu P, Chen SY, Mackenzie C, Stansbury L, DuBose J, Scalea T. **Utility of 3-Dimensional ROC in using vital signs signal for blood transfusion.** Proceeding of 25th IPPR Conference on computer Vision, Graphics and Image Processing.

Slaughter G, Kurtz Z, desJardins M, Hu PF , Mackenzie C, Stansbury L, Stein D, **Prediction of Mortality** Proceeding of 2012 IEEE Biomedical Circuits & Systems Conference,

Oates T, Mackenzie C, Stein D, Stansbury L,DuBose J, Aarabi B,Hu PF **Exploiting Representational Diversity for Time Series Classification** Proceeding of IEEE 11th International Conference on Machine Learning and applications (ICMLA 2012)

Oates T, Mackenzie C, Stansbury L, Aarabi B, Stein D, Hu PF **Predicting Patient Outcomes from a Few Hours of High Resolution Vital Signs Data** Proceeding of IEEE 11th International Conference on Machine Learning and applications (ICMLA 2012

Kalpakis K, Yang S, Hu P, Mackenzie C, Stansbury L,Stein D, Scalea T. **Outcome prediction for patients with severe traumatic brain injury using permutation entropy analysis of electronic vital signs data.** Proceeding of Machine Learning and Data Mining MLDM´2012 Conference

Yang S, Kalpakis K, Mackenzie C,Stansbury L, Stein D, Scalea T, Hu PF. **Online recovery of missing values in vital signs data streams using low-rank matrix completion** Proceeding of IEEE 11th International Conference on Machine Learning and applications (ICMLA 2012)

Journals

Kahraman S, Dutton RP, Hu P, Xiao Y, Aarabi B, Stein DM, Scalea TM **Automated Measurement of "Pressure Times Time Dose" of Intracranial Hypertension Best Predicts Outcome After Severe Traumatic Brain Injury.** J Trauma 2010; 69(1):110-118.

Kahraman S, Stansbury L, Hu P, Xiao Y, Stein DM, Scalea TM. **Heart rate and pulse pressure variability are associated with intractable intracranial hypertension after severe traumatic brain injury.** Journal of Neurosurgical Anesthesiology 2010; 22(4):296-302.

Kahraman S, Stein D, Hu P, Stansbury L, Hess J, Xiao Y, Dutton R, Scalea T. **Dynamic three-dimensional scoring of cerebral perfusion pressure and intracranial pressure provides a Brain Trauma Index that predicts outcome in patients with severe TBI.**. J Trauma. 2011; 70(3):547-553.

Stein DM, Kufera JA, Lindell A, Murdock KR, Menaker J, Bochicchio GV, Aarabi B, Scalea TM. **Association of CSF biomarkers and secondary insults following severe traumatic brain injury**. Neurocrit Care 2011:14(2):200-207.

Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Keledjian K, Bochicchio GV, Aarabi B, Scalea TM. **Relationship of serum and CSF biomarkers to intracranial hypertension and cerebral hypoperfusion following severe traumatic brain injury.** J Trauma. 2011; 70(5):1096-103

Stein D, Hu PF, Brenner M, Sheth K, Aarabi B, Scalea TM. **Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome following severe traumatic brain injury.** J Trauma 2011; 71(2):364-374.

Fitzgerald M, Cameron P, Mackenzie C et al. **Trauma Resuscitation Errors and Computer Assisted Decision Support.** Arch Surg 2011:146(2):2118-225.

Jhuo J, Xu S, Porter J, Mullins R, Simon JZ, Fiskum G, Gullapalli RP. **Diffusion kurtosis as an in vivo imaging marker for reactive astrogliosis in traumatic brain injury.** NeuroImage (2011), doi:10.1016/j.neuroimage.2011.07.050.

Woodford MR, Mackenzie CF, DuBose J, Hu P, Kufera J, Hu E, Dutton RP, Scalea TM. **Continuously Recorded SpO2 and Heart Rate During Pre-Hospital Transport Outperform Initial Measurement in Prediction of Mortality after Trauma.** J Trauma Acute Care Surg. 2012 Apr;72(4):1006-12.

Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM **Traditional systolic blood pressure targets underestimate hypotension-induced secondary brain injury** J Trauma Acute Care Surg. 2012 May;72(5):1135-9

Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, Aarabi B, Scalea TM **Use of serum biomarkers to predict cerebral hypoxia following severe traumatic brain injury**. Journal of Neurotrauma. Apr 10, 2012; 29:1140-1149

Stein DM, Lindell A, Murdock KR, Kufera JA, Menaker J, Scalea TM **Use of serum biomarkers to predict secondary insults following severe traumatic brain injury**. Shock. 2012 Jun;37(6):563-8

Brenner M, Stein D, Hu P, Kufera J, Woodford M, Scalea T. **Association between early hyperoxia and worse outcomes after traumatic brain injury.** Arch Surg. 2012 Jul 16:1-15

Stein DM, Hu P, Chen H, Stansbury LG, Yang S, Scalea TM. **Computational "gene-mapping" to analyze continuous automated physiologic monitoring data in neuro-trauma intensive care.** J Trauma Acute Care Surg. 2012 Aug:73(2):419-425.

Stein D, Brenner M, Hu P, Yang S, Hall E, Stansbury L, Menaker J, Scalea T. **Timing of Intracranial Hypertension following Severe Traumatic Brain Injury.** Neurocritical Care 2013 Mar 15. (online) 10.1007/s12028-013-9832-3 PMID:23494545

Colton K, Dinardo T, Hu P,Xiong W, Hu E, Reeds G, DuBose J,Stansbury LG, Mackenzie CF, Chiu W, Miller C, Fang R, Stein D, Scalea T, ONPOINT Study Group. **Full of sound and fury, signifying nothing: The burden of transient non-critical monitor alarms in a trauma resuscitation unit**. Journal of Trauma Accepted on Aug 2013.

Hu P, Galvagno SM, Sen A, Dutton RP, Handley C, Shckelford S, Pasley JD, Mackenzie CF. **Identification of dynamic prehospital changes with continuous vital signs acquisition**. Air Med J; Accepted on 10 Sept 2013

CONCLUSIONS

At the conclusion of Year 6 significant progress has been made toward meeting overall project milestones. The infrastructure of staff, technology and data management had been created to support the completion of sub-projects and long-term assessment of TBI patients. The robust Brain Resuscitation Registry (BRR) needed to accomplish the goals of this multi-year project has been implemented and continues to undergo refinement especially in terms of reporting. Recruitment and data collection for the Vital Signs human sub-projects are completed and data analysis and prediction model development are complete for this project. New funding has been pursued to continue the efforts. Sub-project 2, Cytokines has completed subject recruitment and follow-up, specimen processing and data analysis. Both animal sub-projects have been completed and analysis finalized. Two retrospective human sub-projects have been completed and manuscripts submitted and/or published detailing the results. The protocol for the final new human use sub-project has been approved and after managing multiple challenges associated with initiation of this project, subject enrollment and data collection have been the primary focus of the final 20 month no-cost extension to conclude in May 2014.

REFERENCES

No new literature searches have been undertaken during Year 6 of this project.

APPENDICES

Abstracts Accepted or Presented since last Annual Report

Prediction of Mortality

Slaughter G, Kurtz Z, desJardins M, Hu PF, Mackenzie C, Stansbury L, Stein DM.
2012 IEEE Biomedical Circuits & Systems conference, Nov 28-30, Taiwan

Abstract— Real-time patient monitoring data collected over the course of trauma care are often large in quantities and require systematic representation that can combined temporal reasoning and validated algorithms to support clinical decision making. Available continuous vital signs, in many cases result in few state changes in the temporal range of interest; this work applies validated systematic algorithms to a small set of vital signs data to identify patients at risk for mortality. Vital signs signals are used to train J48, naïve bayes, decision stump and SMO models. The InfoGain features selection algorithm was used to extract the best features using full run time-series data and feature generation permitted the features to be trained/tested on sensor data of any size, which dramatically improved the prediction classification of the J48 algorithm. The evaluation of the models were done using leave-one-out cross validation. The quality of the classification was determined by the accuracy, precision and recall. Results show that the J48 algorithm coupled with feature selection is a simple method for the identification of patients at increased risk for mortality in trauma care.

Exploiting Representational Diversity for Time Series Classification

Oates T, Mackenzie CF, Stein DM, Stansbury LG, DuBose J, Aarabi B, Hu P.
ICMLA(International Conference on Machine Learning and Applications) 2012: Machine Learning Ensemble Methods and Applications track, December, Boca Raton, FL

Abstract—More than a decade of research has produced numerous representations and similarity measures to support time series classification and clustering. Yet most of the work in the field is so focused on the representation or similarity measure that it ignores the possibility of improving performance using ensembles of representations or classifiers. This paper explores ways of exploiting representational diversity for time series classification via ensembles of representations. We focus on the Symbolic Aggregate approXimation (SAX) discretization method coupled with the bag-of-patterns (BoP) representation because of their state-of-the-art performance in the single representation/ classifier case. Experiments with a number of standard benchmark time series datasets and a new dataset of vital signs collected from patients suffering from traumatic brain injury demonstrate the power of the ensemble approaches, producing a single method that is often significantly better than vanilla SAX/BoP and compares favorably on a per dataset basis with the best methods reported in the literature for each dataset.

Predicting Patient Outcomes from a Few Hours of High Resolution Vital Signs Data

Oates T, Mackenzie CF, Stansbury LG, Aarabi B, Stein DM, Hu P.

ICMLA(International Conference on Machine Learning and Applications) 2012: Machine Learning Ensemble Methods and Applications track, December, Boca Raton, FL

Abstract—Monitoring of non-invasive, continuous, high resolution patient vital signs (VS) such as heart rate and oxygen saturation is becoming increasingly common in hospital settings.
These data are a potential boon for health informatics as a source of predictive information about a variety of patient outcomes. Yet the volume, noisiness, and per-patient idiosyncrasies of these data make their use extremely challenging. This paper explores the utility of representing VS data as unordered collections (bags) of local discrete patterns for the purpose of training classifiers to predict outcomes for traumatic brain injury patients, including mortality and level of cognitive function months after hospital discharge. The Symbolic Aggregate approXimation (SAX) algorithm is used for discretization, producing a bag of SAX words (local patterns) for each time series. Experiments with a dataset of sixty traumatic brain injury patients demonstrate that this approach is promising both in terms of predictive accuracy and patterns that it can reveal in the underlying VS data.

Summary of Staff, Roles and Percent Effort by Project/Sub-project

STAFF MEMBER	ROLE	% FUNDED EFFORT (%FTE)
Thomas Scalea	PI	0
Lisa Gettings	Administrator	0
Karen Murdock	Project Manager	0
Colin Mackenzie	Sub-Project PI; Vital Signs study	donated
Peter Hu	Co-Investigator	0
Yan Xiao (resigned)	Technical Support	0
Steven Seebode (resigned 10/6/10)	Technical Support	0
George Hagegeorge (hired 2/28/11)	Technical Support	0
Jessica Baroody	Technical Support	0
Shiming Yang	Student Assistant	0
Eric Lund	IT Application Engineer	0
Deborah Stein	Sub-project PI; Cytokine study	0
Kevin Sheth	Sub-project Co-PI	1
Bizhan Aarabi	Co-Investigator	0
Richard Dutton	Co-Investigator	0
Allison Lindell (resigned 7/30/11/0	Coordinator; Cytokines study	0
Kaspar Keledjian	Cytokine technician	0
Robert Rosenthal	Sub-project PI; Animal model	0
Gary Fiskum	Co-Investigator	0
Karen Volpini	Database Management	0
Madeline Mitrou (resigned 1/1/11)	Research Nurse	0
Yawei Wang	Research Nurse	0
Amechi Anozado	Research Assistant	0
Margaret Mensa	Research Nurse	0
Diane Rouse (resigned)	Research Nurse	0
Marianne Hattan	Research Nurse	0
Bonnie McManus (resigned 6/23/11)	Research Nurse	0
Keri Volpini	Research Assistant	0
Christine Wade-Mariani	Research Assistant	0
Charles Simpson (resigned)	Research Assistant	0
Scott Berry (resigned)	Research Assistant	0
Tondeleyo Gonzalez	Research Assistant	0
Carrie Sauer (resigned)	Research Assistant	0
Olga Kolesnik	Research Assistant	0

Sean Jordan (resigned)	Research Assistant	0
Sara Wade	Research Assistant	0
David Prakash (resigned 12/31/10)	Research Assistant	0
Ryan Gens (resigned)	Research Assistant	0
Cris Imle	Physical Therapist	0
Myra Collins (resigned 7/13/10)	Research Assistant	0
Jonathan Gooch	Research Assistant	0
Sean Crane	Research Assistant	0
Daniel Mayer	Research Assistant	0
Jamila Torain (hired 2/15/11)	Research Assistant	0
Emily Cooper (hired 1/18/11)	Research Assistant	0
Genna McFarland (resigned)	Student Assistant	0
Kristina Clem (resigned)	Data Entry	0
Joe Kufera	Statistician	0
Gordon Smith	Epidemiologist	0
Julie Hazleton	Technician	0
Jennifer Racz (resigned)	Technician	0
Xiaoli Xiao (resigned)	GRA	0
Wei Xiong (resigned 12/31/10)	GRA	0
Keng-Hao Liu	GRA	0
Tiffany Greco	GRA	0
Yu Wei Chang (resigned)	Data Processor	0
Ryan Seebode	Data Entry Assistant	0
Susanna Scafidi	Co-Investigator	0
Matthew Woodford (resigned 12/15/10)	Post-doctoral Fellow	0
Irina Balan	Post-doctoral Fellow	0
Rao Gulliapalli	Co-Investigator	0
Matt Lissauer	Co-Investigator	0
Jiachen Zhuo	Post-doctoral Fellow	0
Josh Ayres	Student Assistant	0
Lynn Stansbury	Medical Editor	0

* 100% effort for a GRA is 20 hours/week

Contract Expenditures to Date

COST ELEMENTS	CURRENT PERIOD	YEAR 6 TOTAL	YEAR 5 TOTAL	YEAR 4 TOTAL	YEAR 3 TOTAL	YEAR 2 TOTAL	YEAR 1 TOTAL	PROJECT CUMULATIVE TOTAL
Personnel	$0	($116)	$40,372	$957,170	$913,538	$1,239,701	$477,416	$3,628,081
Fringe Benefits	$0	($9)	$5,739	$168,605	$148,395	$217,915	$75,619	$616,264
Supplies	$0	$12	$9,840	$94,847	$98,577	$58,499	$18,363	$280,139
Equipment	$0	$0	$0	$50,583	$11,897	$14,898	$22,125	$99,503
Travel	$0	$0	$1,282	$4,450	$3,503	$3,330	$1,578	$14,143
Other Direct Costs	$9,350	$41,217	$20,125	$27,818	$12,843	$18,145	$2,070	$120,009
Subtotal	*$9,350*	*$38,895*	$77,358	$1,303,474	$1,188,753	$1,552,487	$597,171	*$4,758,139*
Indirect Costs	*$611*	*$2,963*	$18,288	$321,773	$304,166	$399,045	$149,512	$1,195,747
Fee	*$0*	*$0*	$0	$0	$0	$0	$0	
Total	***$13,887***	***$45,784***	$95,647	$1,625,246	$1,492,919	$1,951,533	$746,683	**$5,953,885**
							Awarded	**$5,939,998**
							Department funded (TCD costs)	**$13,887**

*Includes expenditures through 9/30/13

Quarterly Report

1. **Award No.:** 06172002
2. **Report Date:** 10/16/13
3. **Reporting period:** 7/1/13 – 09/30/13
4. **Principal Investigator:** Thomas Scalea, MD
5. **Telephone No.:** 410-328-8976
6. **Award Organization:** University of Maryland Baltimore; R Adams Cowley Shock Trauma Center
7. **Project Title:** Early Support of Intracranial Perfusion
8. **Current staff, role and approximate percent effort of each on project.**

No funded effort for staff (no cost extension year)

Expenses in excess of total awarded amount will be paid by departmental funds as described per NCE request

Progress: ***Sub-project: Vital Signs Data in Trauma Patients***

The annual renewal for this protocol was submitted to UMB IRB in October 2012 and approved for continuation on 10/24/12. The continuing review report was submitted to USAMRMC ORP, HRPO on 12/06/12 and the acceptance memorandum was received on 12/07/12. The annual renewal for the upcoming year, was be submitted to UMB IRB in early October 2013 and approval is pending.

Data collection and analysis for this sub-project are now complete. Final abstracts and manuscripts are in process. We anticipate closing the IRB protocol for this project by the end of the year.

Progress: ***Sub-project: Cytokines***

The last annual renewal for this protocol was submitted to UMB IRB on 01/17/12 and approved for continuation on 01/19/12. The continuing review report was submitted to USAMRMC ORP, HRPO on 03/07/12 and the acceptance memorandum was received on 06/04/12. In December 2012 a closure report was submitted to UMB IRB and the protocol has now been closed.

This sub-project is now complete.

Progress: ***Brain Resuscitation Registry***

The research registry continues to be used for data collection on all patients arriving in the trauma receiving unit and facilitates information exchange between work shifts. Development continues on the reporting “Data Warehouse” that will receive admission and screening data from the research registry and link them to the treatment information and follow up outcomes data, providing an "Incident to Recovery" range of data.

The registry will continue to be used for new research projects in the future as the method for standardizing and evaluating the data collected for the screening process, encompassing virtually all research efforts and not just those under this project.

Progress: **S*ub-projects: Retrospective –***
Traumatic Brain Injury and Fracture Fixation
Traumatic Brain Injury, Oxygenation and Outcomes

Two retrospective sub-projects were designed and submitted to UMB IRB. Both were approved by UMB IRB on 02/24/10 and approved by USAMRMC on 03/29/10. All work has been completed on these sub-projects.

TBI and Fracture Fixation

One abstract based on these analyses has been presented and a manuscript was submitted.

TBI, Oxygenation and Outcomes

Two abstracts have been presented based on this analysis and a manuscript has been published.

Progress: ***Sub- project: Animal models***

All work on this sub-project is completed.

Progress: ***Sub-project: Transcranial Doppler and Brain Acoustic Monitoring***

The annual continuing renewal for this protocol was submitted to UMB IRB in February 2013 and received approval on 02/11/13. The continuing review report was submitted to USAMRMC ORP, HRPO on 03/29/13 and the acceptance memorandum was received on 04/04/13.

Recruitment for this sub-project began on 10/18/12. As of September 30, 2013, 20 have been enrolled; 17 subjects completed at least 5 days of TCD and BAM follow-ups. Two subjects ultimately expired due to their injuries. Follow-up data collection was initiated in February. Thirteen subjects are eligible for 3 month follow-up and to date follow-up data have been successfully obtained on 10 subjects. Nine subjects are eligible for 6 month follow-up and follow-up has been successfully obtained on six subjects thus far.

12. Plans or milestones for the next quarter.

A. Continue enrollment and data collection for TCD and BAM sub-project.
B. Continue 3 and 6 month follow-up data collection for TCD and BAM sub-project.